## REMARKS

Upon entry of this amendment, claims 1-27, 34, 49-52 and new claims 63-77 constitute the pending claims in the present application. Applicants have canceled without prejudice claims 28-33 and 35-48, which are directed to non-elected inventions. Applicants reserve the right to prosecute claims of similar or identical scopes in future applications. Claims 1-27, 34, 49-52, and new claims 63-77 are directed to the elected Group I invention. Among them, claims 7 and 9-11 are directed to non-elected species, and are withdrawn from further consideration.

Applicants submit that new claims 63-77 are supported by the specification including the originally filed claims. Regarding the term "under physiological condition," Applicants submit that this feature is implicitly supported by the specification since the specification teaches culturing of EC cells *in vitro*, which closely proximates physiological growth conditions *in vivo*.

Applicants note that the Office Action asserts that "the record of this Office indicates that claims 1-52 and 54-62 are pending. See the copy of the attached applicant's amendment (Paper No. 7, Jan. 8, 2002." However, upon reviewing the Applicants' record, Applicants can find no evidence that new claims 54-62 were added. If such claims are indeed present in the Office record, please cancel these claims without prejudice. Nevertheless, Applicants have presented new claims starting with claim 63.

Applicants also note that the Office Action states that "claims 7, 9-11, **28**, 54-62, and 35-48" are withdrawn from consideration," while it appears that "claims 7, 9-11, **28-33**, and 35-48" should be withdrawn from consideration.

Applicants respectfully request reconsideration in view of the following remarks. Issues raised by the Examiner will be addressed below in the order they appear in the Office Action.

*Claim objections*

The Office Action asserts that the numbering of new claims is not in accordance with 37 CFR 1.126. Specifically, the Office Action states that "[m]isnumbered claims 81-89 have been renumbered 54-62."

As stated above, if for some reason claims 54-62 are present in the Office record, please cancel these claims without prejudice. Reconsideration and withdrawal of this objection is respectfully requested.

*Specification objections*

The Office Action also objects to the specification as containing amino acid sequences without sequence identifiers. Accordingly, Applicants have reviewed and amended the specification in whole (including the drawings) to include proper sequence identifiers, thereby obviating this objection. Applicants have also submitted a sequence listing under 37 CFR 1.821-1.825 and formal drawings for Figure 2 and 5, with sequence identifiers labeled. Reconsideration and withdrawal of this objection is respectfully requested.

*Claim rejections under 35 U.S.C. 112, second paragraph*

Claims 1-6, 8, 12-27, 34, and 49-53 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite since claims 1-3 recite "the chimeric peptide" which does not have sufficient antecedent basis. Applicants have amended claims 1-3 to obviate this rejection. Reconsideration and withdrawal of this rejection is respectfully requested.

*Claim rejections under 35 U.S.C. 102*

Claims 1-6, 8, 12-27, and 34 are rejected under 35 U.S.C. 102(b), as being anticipated by WO 95/30759 ("'759" thereafter) as evidenced by Zetter and by Fixe.

Specifically, the Office Action asserts that '759 teaches that chimeric polypeptide with a useful heterologous peptide inserted anywhere within serum albumin (SA) can be derived from various therapeutically useful proteins, including an angiogenesis-inhibiting protein or a protein that binds to receptor tyrosine kinase (RTK). The '759 application allegedly also teaches chimeras with increased *in vivo* stability. The Office Action acknowledges that '759 does not specify the functional property of the various useful proteins, a laundry list of functional properties are listed in pages 3 and 4, also in claim 3 of '759. Thus the Office Action concludes that the functional properties are inherent properties of the useful proteins. To support this, the Office Action also refers to Fixe to show that it is well-known in the art that M-CSF is a RTK

(note: should be "ligand for RTK"), and that an active portion of M-CSF inserted into the SA protein would bind to a cell surface receptor or RTK. Similarly, the Office Action refers to Zetter which shows that angiostatin and endostatin are well-known in the art as angiogenesis-inhibiting proteins useful for cancer treatment.

Applicants submit that the claimed invention is directed to a chimeric SA polypeptide that "exhibits increased biological activity to the heterologous peptide sequence itself" (emphasis added). The instant specification teaches that the chimeric polypeptide of the claimed invention exhibits increased biological activity when compared to the uninserted heterologous peptide itself. For example, on page 41, first paragraph, the specification indicates that the EC binding peptides inserted into mouse serum albumin actually exhibit 1000-fold more activity than the uninserted synthetic peptides themselves. The chimeric polypeptide is effective in inhibiting EC cell proliferation at nM concentrations, while the uninserted peptide is effective only in the mM range. In contrast, the '759 application is completely silent about increased biological activity. It merely *hoped* that a chimeric polypeptide may possess enhanced stability (Applicants note that Example 8 only shows that an inserted short peptide is *accessible* to a protease, but is otherwise silent to the stability of the chimeric peptide). Even assuming, for the sake of argument, that what the '759 application suggests is true, enhanced activity is still quite different from increased biological activity, as claimed in the instant application. As a skilled artisan would appreciate, two otherwise identical polypeptides may have the same stability (for example, life-span in serum), but can have dramatically different overall biological activities, no less potencies, due to factors such as conformation in a specific solution. The '759 application also fails to describe any assay or even intention of comparing biological activity between inserted heterologous peptide and the uninserted counterpart, thus failing to put the claimed invention in possession of the public, as is legally required for anticipation (see below). Reference to Zetter or Fixe does not correct this defect.

Applicants further submit that the '759 application fails to anticipate the new claims directed to chimeric polypeptides that bind cell surface receptors under physiological conditions. In that respect, the '759 application is not even enabled for chimeric polypeptides that bind cell surface receptors under physiological conditions.

As a skilled artisan would appreciate, human serum albumin (HSA) is a protein of 66.5 kDa that is composed of three homologous domains, each of which displays specific structural and functional characteristics. HSA is known to undergo different pH-dependent structural transitions, the N-F and F-E transitions in the acid pH region and the N-B transition at slightly alkaline pH. Reviewed in Carter *et al.* (1994) Adv. Protein Chem. 45, 153-203 (cited by the instant Office Action below); and Peters, T., Jr. (1996) All About Albumin: Biochemistry, Genetics, and Medical Applications, Academic Press, Inc., New York.

E <-------> F <-------> N <-------> B <-------> A

| | | | | | |
|---|---|---|---|---|---|
| pH of transition: | 2.7 | | 4.3 | 8 | 10 |
| Name: | **E**xpanded | **F**ast | **N**ormal | **B**asic | **A**ged |
| % Helix: | 35 | 45 | 55 | 48 | 48 |

Adapted from Carter *et al.*, *supra.*

The N-F transition involves the unfolding of domain III. The F form is characterized by a dramatic increase in viscosity, much lower solubility, and a significant loss in helical content. At pH values lower than 4, albumin undergoes another expansion with a loss of the intra-domain helices of domain I which is connected to helix of domain II, and that of helix of domain II connected to helix of domain III. This expanded form is known as the (E) form which has an increased intrinsic viscosity, and a rise in the hydrodynamic axial ratio from about 4 to 9. In the pH region of the N-B transition, domain I and domain II experience a tertiary structural isomerization.

The only working examples of the '759 application are limited to the demonstration that a heterologous peptide inserted in an albumin protein can serve as a *substrate* for protease cleavage, under the non-physiological *in vitro* condition of pH 8.0 (which is about 10-times more basic as compared to the normal or physiological pH value of about 7. See page 30 of '759). At that pH, wild-type albumin undergoes the N-B transition. The B isomerization is understood as a structural fluctuation, a loosening of the molecule with loss of rigidity. Wilting *et al.* (1979) Biochim. Biophys. Acta 579:469-473; Bos *et al.* (1988) Biochem. Pharmacol. 37:3905-3909; and

Bos *et al.* (1988) Biochim. Biophys. Acta 953: 37-47. Enzymes are generally able to tolerate, and in some cases are optimized for, substrate sequences in a protein that are present in a random coil configuration rather than part of a more rigid structural domain. Accordingly, under the circumstances, one skilled in the art would likely be skeptical about the general applicability of chimeric albumin proteins even for other protein-protein interactions under discrete non-physiological aqueous conditions, let alone interactions at a cell surface.

"It is well-settled that prior art under 35 U.S.C. 102(b) must sufficiently describe the claimed invention to have placed the public in possession of it. Such possession is effected if one of ordinary skill in the art could have combined the publication's description of the invention with his own knowledge to make the claimed invention. Accordingly, even if the claimed invention is disclosed in a printed publication, that disclosure will not suffice as prior art if it was not enabling" (emphasis added), *In re Donahue*, 766 F.2d 531226 USPQ 619 (Fed. Cir. 1985). Also see *Chester v. Miller*, 906 F.2d 1574, 15 USPQ2d 1333 (Fed. Cir. 1990). In addition, "...a prior art reference must be 'considered together with the knowledge of one of ordinary skill in the pertinent art.'" *In re Paulsen*, 30 F.3d 1475, 31 USPQ2d 1671 (Fed. Cir. 1994).

Applicants submit the criteria set forth above are what separate invention from science fiction. Applicants submit that a skilled artisan could not have combined the disclosure of the '759 application with the common knowledge about SA conformation in solution to make the claimed invention. Thus, the '759 application fails to place the public in possession of the claimed invention. Specifically, if a skilled artisan were to combine the disclosure of the '759 application and the well-known knowledge that SA undergoes conformational changes under different pH conditions, the skilled artisan would not be certain if the SA chimera containing the inserted factor Xa substrate would still be cleavable by Xa under physiological conditions, let alone be certain about inserting any of the laundry list of potential insertable heterologous peptides into SA while retaining their biological activity, such as ability to bind to a cell. It is the instant application that first discloses that an inserted heterologous peptide maintains its cell surface-binding ability and growth inhibitory activity under physiological conditions, thus truly overcoming the prior art concern of SA conformation change and enabling a skilled artisan to practice the claimed invention.

"Anticipation" in the patent sense means that the subject matter was previously known. A mere suggestion of general procedures that *may or may not succeed* in producing a novel product does not convert the suggested product into a previously existing product. This is especially so when the common knowledge at the time contradicted the prediction of a cited "prior art" reference.

Until Applicants demonstrated that the chimeric albumins could indeed interact with whole cells and induce biological responses as a consequence to the interaction, a skilled artisan would not know whether the inserted heterologous peptide described in the '759 application would *certainly* (rather than *probably* or *possibly*) be able to bind a cell surface receptor in view of the prior art knowledge of SA conformation changes at different pH conditions (such as the normal or physiological pH of about 7). This is further complicated by the microenvironment surrounding the cell surface (see below). The skilled artisan would not have been certain that an inserted heterologous peptide would still be able to bind a cell surface receptor and inhibit a biological response at normal pH.

It is undisputed that '759 does not disclose a chimera that would bind to cell surface under normal or physiological conditions. In view of common knowledge in the art at the time of filing, a skilled artisan would be unable to predict whether a chimera made according to the disclosure of '759 would bind to a cell surface under physiological conditions. A general recipe of uncertain reliability is nothing more than an invitation for further experimentation with no assurance of success, and it does not convert a hoped-for product into one that previously existed.

From a different perspective, the disclosure of '759 must satisfy the enablement requirement of 35 U.S.C. 112, first paragraph, for this reference to qualify as prior art. The test for enablement is whether a skilled artisan, in view of the disclosure of the specification and common knowledge in the field, can practice the claimed invention without undue experimentation. Factors to be considered in assessing enablement are set forth in *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), and include state of the art, level of predictability, existence of working examples, amount of direction or guidance by the inventor, etc.

After analyzing such factors relating to enablement, the disclosure of '759 is clearly non-enabling for any embodiment within the scope of the pending claims, since the state of the art (SA undergoes conformation change at physiological pH as compared to the tested pH 8.0) casts a significant doubt on the *in vivo* treatment method disclosed in the '759 application. A skilled artisan would face utter unpredictability when practicing the *in vivo* method of '759, especially in view of the fact that '759 provides no working example and barely any guidance for making or testing biologically active chimeric proteins . Thus, undue experimentation would be needed to practice the any embodiment of '759 that would anticipate the pending claims.

Therefore, the '759 application does not explicitly, implicitly, or inherently teach or suggest each and every aspect of the claimed invention, and cannot anticipate the claimed invention. Reconsideration and withdrawal of the rejection are respectfully requested.

*Claim rejections under 35 U.S.C. 103(a)*

Claims 49-52 are rejected under 35 U.S.C. 103(a) as being unpatentable over '759 as applied to claims 1 and 23 above, further in view of Carter *et al.*

Specifically, '759 allegedly teaches that any therapeutically desirable peptide can be inserted into anywhere within SA, resulting in a chimeric peptide more useful as a pharmaceutical since it is more stable and lasts longer *in vivo*, so that "[t]his property can reduce frequency of painful injections." However, the Office Action acknowledges that '759 does not specifically teach insertion of the heterologous peptide into a portion of a Cys loop of a SA protein. The Office Action also alleges that '759 teaches in Figure 1 that SA has extensive Cys loops, and that Carter teaches the crystal structure of SA with "several surface exposed cysteine loops (see page 167-173, Fig. 10 along with Table II)." Applicants respectfully disagree.

Pursuant to MPEP 2142, "[t]o establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the

reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. Using the Applicants' disclosure as a template for picking and choosing from amongst the prior art to reconstruct the claimed invention is not permitted. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991)." Thus, to render the claimed invention obvious, all three criteria must be met.

Regarding the insertion site, the '759 application suggests that the heterologous peptide may be inserted into sites that "are preferably localized in the regions of the albumin presumed to form exposed regions at the surface of the molecule, these regions preferably being loops" (page 7, lines 3-5). However, contrary to the Office Action's assertion, the '759 application never teaches or suggests that any of these sites could be cysteine loops as claimed in the instant application. In fact, the '759 application does not refer to any cysteine loops at all. Instead, the '759 application suggested a few preferred insertion sites as "residues 57-62 (region 5) which corresponds to a loop connecting helices h3 and h4; residues 103-120 which corresponds to the zone between subdomains (region 8, an alpha helix structure, not a loop at all); residues 178-200 which corresponds to a helix (region 13, another alpha helix, not a loop at all); and residues 419-430 which corresponds to a region defined by helices h2 and h3 of domain III (not a Cys loop). Aside from region 5, which partially overlaps with one of the claimed Cys loops, none of these preferred sites actually corresponds to any of the claimed Cys loops. Even though the '759 application suggests that the insertion sites are preferably exposed surface loops, there are many different surface loops in the SA structure. This genus of "exposed surface loop structure" does not anticipate the claimed Cys loops, one particular species of the exposed surface loops. Neither would this genus of loops specifically suggest that a skilled artisan look for Cys loops on the surface of SA. The advantage of the Cys loop, first recognized by the present inventors, partly resides in the fact that these loops are structurally constrained by the disulfide bonds forming these loops, and thus a peptide inserted within the Cys loop is much less likely to disrupt the overall structure of the chimeric protein, while a peptide inserted in a non-constrained loop or helix structure are more likely to disrupt the overall structure and/or stability of the chimera. This concept was neither taught nor suggested by the '759 application. In fact, Figure 1 of '759 actually shows many potential loop-like structures between the helices. These loops are not necessarily linked by disulfide bonds (see, for example, the loops between h2 and h3, between h6 and region 8, between region 8 and h7, etc.).

On the other hand, Carter is a review article relating to the structure of SA. In the passage cited by the Office Action (pages 167-173, Figure 10 and Table II), Applicants were unable to find any specific reference to "surface exposed cysteine loops," as recited in the Office Action. The only passages relating to the "Cys loop" seem to be descriptions for "disulfide bridges" (see page 169, last line; several occurrences on page 170; and page 171, section "b"). But none of these passages seems to indicate that any Cys loops are actually "surface exposed," let alone suitable to serve as potential insertion sites for heterologous proteins. Thus Carter also does not suggest Cys-constrained surface-exposed loops claimed in the instant application.

In view of this, even if a skilled artisan is motivated to combine '759 and Carter, the artisan would not specifically look for Cys loops as claimed in the instant application. Thus the combined teaching of '759 and Carter still fails to guide a skilled artisan to arrive at the claimed invention, and does not teach or suggest all the limitations of the claimed invention.

Applicants further submit that a skilled artisan would also lack reasonable expectation of success in arriving at the claimed invention.

First of all, the cited art disclosed fusion of heterologous peptides to either the N- or C-terminus of SA, but, except for the '759 application, not insertion of heterologous peptides into the SA. But none of these references teach or suggest that an inserted heterologous peptide may have increased biological activity compared to the uninserted counterpart. Thus, a skilled artisan would have no reasonable expectation that an inserted heterologous peptide would show *increased* biological activity.

Secondly, Applicants further submit that the '759 application does not render obvious the new claims directed to chimeric polypeptides that bind to cell surface receptor proteins and/or inhibit an intracellular signaling pathway (such as cell proliferation signaling), for the reasons below.

As discussed above, SA undergoes conformational changes in solutions of different pH .

Applicants submit that the teachings of the '759 application do not render obvious any pending claims in the instant application that are directed to chimeric albumin proteins with inserted heterologous peptides, and which bind to a cell and induce or inhibit an intracellular

signal pathway in the cell. Until Applicants demonstrated that the chimeric albumins could indeed interact with whole cells and induce biological responses as a consequence to the interaction, a skilled artisan would have no reasonable expectation that the inserted heterologous peptide described in the '759 application would be able to bind a cell surface receptor in view of the prior art knowledge of SA conformation changes at different pH conditions (such as the normal or physiological pH of about 7). This is further complicated by the microenvironment surrounding the cell surface (see below). It would not be obvious to a skilled artisan that an inserted heterologous peptide would still be able to bind a cell surface receptor and inhibit a biological response at normal pH.

As discussed above, the only working examples of the '759 application are limited to the demonstration that a heterologous peptide inserted in an albumin protein can serve as a *substrate* for protease cleavage. However, in general, the interaction of two discrete and purified molecules in water is not predictive of whether those same molecules would be able to interact in a context where one is displayed as part of a complex on cell surface.

The microenvironment surrounding cells is unique from an external aqueous milieu. The lipid/water interface at which the interaction of a chimeric albumin with cell surface molecules occurs can effect protein folding and protein interactions by altering, for example, protonation of amino acid side chains, hydrophobic and ionic interactions and the like. Without the benefit of Applicants' experimental results, one skilled in the art could reasonably conclude that such effects on protein structure and protein-protein, protein-lipid or protein-carbohydrate interactions may negatively effect the ability of the chimeric albumin proteins taught by the '759 application to interact with whole cells in any biologically relevant manner. That is, while the '759 application may make it obvious to try to make chimeric albumin proteins with whole cell activity (invitation for further experimentation), it would not be obvious from the teachings of the '759 application ("prior art") that those chimeric proteins would in fact work as intended.

Accordingly, despite the generic teachings of the '759 application, the ability of the chimeric albumin proteins claimed in the instant application to interact with whole cells in any biologically meaningful manner (such as under physiological condition) was neither taught nor suggested in the prior art. Thus a skilled artisan would have no reasonable expectation of success

in arriving at the claimed invention. In other words, until Applicants demonstrated that the chimeric albumins could indeed interact with whole cells and induce biological responses as a consequence to the interaction, *a priori*, one of ordinary skill in the art would not have had a reasonable expectation for success based on the teachings of the '759 application and the knowledge available in the prior art. For the same reason, the skilled artisan would also lack motivation to insert heterologous peptides into constrained Cys loop sites, since the natural conformation of the inserted peptide might be too distorted to maintain activity.

The Office Action also asserts that there was tremendous interest in the scientific community to develop pharmaceuticals using serum albumin (pages 194-195), thus rendering the claimed invention obvious. Applicants submit that a general motivation to improve the prior art is very different from a specific motivation to improve the prior art in a way that would result in Applicants' invention in particular.

In view of the foregoing, Applicants submit that all three requirements for making a *prima facie* case of obviousness are not met. Accordingly, reconsideration and withdrawal of rejection under 35 U.S.C. 103(a) is respectfully requested.

## CONCLUSION

For the foregoing reasons, Applicants respectfully request reconsideration and withdrawal of the pending rejections. Applicants believe that the claims are now in condition for allowance and early notification to this effect is earnestly solicited. Any questions arising from this submission may be directed to the undersigned at (617) 951-7000.

If there are any other fees due in connection with the filing of this submission, please charge the fees to our **Deposit Account No. 18-1945.** If a fee is required for an extension of time under 37 C.F.R. § 1.136 not accounted for above, such an extension is requested and the fee should also be charged to our Deposit account.

Respectfully Submitted,

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